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Original Article

Development and evaluation of emulgel formulation of dexketoprofen trometamol

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Abstract:- Emulgel is a combinational formulation consisting of emulsion and gel and the type of combination depends upon the nature of drug so that maximum bioavailability can be achieved. The benefits of Emulgel over the traditional topical administration include thixotropic, greaseless, improved spreadibility, easily removable, biodegradable, emollient, and better convenience. Along with this, high stability and improved shelf life of Emulgel is also encouraging the researchers to develop new products belonging to this class. Currently, the available topical drug administration technologies are able to deliver the hydrophilic drugs only and the inability to deliver the hydrophobic drugs is one of the major limitations for this approach. Dexketoprofen trometamol appears to provide similar analgesic efficacy to COX-2 inhibitors when used to treat acute pain, has a rapid onset of action, is well tolerated, and has an opioid-sparing effect when used as part of a multimodal regimen in the acute pain setting. Emulgel was concluded to be a successful dosage form for topical delivery of drugs. Out of all the prepared formulations, F5 was found to have the best release rate and maximum drug content

KEYWORDS: Cox-2 inhibitor, emulgel, dexketoprofen, spreadibility, permeation

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Introduction: The skin, as the largest sensory organ in the human body, plays a pivotal role in several essential functions while serving as the first-line barrier against external influences. It accounts for approximately 10% of the total body mass and boasts an average surface area of 1.7 square meters[(1).] Beyond its protective function, the skin exhibits a remarkable capacity to absorb topically applied ingredients, making it an increasingly accepted and advantageous route for delivering a variety of pharmaceutical compounds[(2)]. The structure of the skin facilitates the penetration of topically applied substances into various skin layers and, in some cases, into systemic circulation. Most substances penetrate the skin through three primary pathways: the stratum corneum, sweat ducts, and sebaceous follicles. In recent years, topical drug delivery has emerged as a novel and highly effective approach for managing a range of serious medical complications[(3).] This approach proves particularly valuable when conventional drug delivery routes fail to provide the desired therapeutic response. Furthermore, the topical route excels in targeting localized skin infections, such as fungal or bacterial skin conditions. The topical drug delivery system encompasses various dosage forms designed for application to the skin, offering an ideal alternative for addressing skin disorders and localized treatment. Notably, this system presents the distinct advantage of bypassing first-pass metabolism, which can significantly alter drug efficacy. Moreover, it mitigates the risks and inconveniences associated with intravenous route therapy [(4).] Topical formulations are available in diverse consistencies, including solid, semisolid, and liquid forms, further enhancing their adaptability and utility in healthcare and pharmaceutical applications [(5)] .

2. Material and Methods. Emcure pharmaceuticals ltd. gandhinagar, gujrat, INDIA provided dexketoprofen trometamol as a given sample.

Formulation of Emulgel Batches of Dexketoprofen Trometamol The gel in formulation was prepared by dispersing polymer in purified water with constant stirring at a moderate speed then the pH adjusted to 6-6.5 using Tri Ethanol Amine (TEA). The oil phase of the emulsion was prepared by dissolving span 80 in liquid paraffin and aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl paraben and propyl paraben were dissolved in propylene glycol whereas the drug was dissolved in ethanol and both solutions were mixed in aqueous phase. Menthol oil was added to oil phase which acts as a penetration enhancer. Both oil phase and aqueous phase were separately heated to 40° to 50°C then oily phase was added to aqueous phase with constant stirring until cooled to room temperature. Different batches of emulgel formulations were prepared using different quantities of polymers to determine the best polymer ratio for the present investigation work.

Table-1: Emulgel formulation of Dexketoprofen trometrol

S.No.	Ingredients	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Dexketoprofen trometamol (mg)	20	20	20	20	20	20
2	HPMC (%)	2.5	5	-	-	-	-
3	Carbopol 934p (%)	-	-	2.5	5	-	-
4	Carbopol +HPMC (%)	-	-	-	-	1:1	1:2
5	Span 80 (%)	1	1	1	1	1	1
6	Tween 80 (%)	1	1	1	1	1	1
7	Liquid paraffin(%)	7.5	7.5	7.5	7.5	7.5	7.5
8	Propylene glycol(%)	7.5	7.5	7.5	7.5	7.5	7.5
9	Methyl paraben(%)	0.5	0.5	0.5	0.5	0.5	0.5
10	Propyl paraben(%)	0.5	0.5	0.5	0.5	0.5	0.5
11	Ethanol (%)	5	5	5	5	5	5
12	Menthol oil (%)	1	1	1	1	1	1
13	Water (ml)(q.s.)	50	50	50	50	50	50

2.1 Evaluation of Formulated Emulgel Batches

The formulated emulgel batches of Dexketoprofen trometamol were evaluated for the following chemical properties: -

2.1.1 Physical parameters

Homogeneity, Colour, texture, odor, phase separation of the prepared gels were tested by visual examination.

2.1.2 Measurement of pH

The pH of Dexketoprofen trometamol gels were determined by using a calibrated pH meter. The readings were taken for an average of three samples. The pH meter was calibrated before each use with standard 4, 7 and 9 pH buffer solutions respectively88.

2.1.3 Viscosity

A Brookfield digital viscometer with a suitable sample adaptor was used to measure the viscosities of the emulgels in cps. All the measurements were conducted using spindle no.6 using about 100 ml sample volume at 50 RPM. Direct multiplication of the dial readings with factors given in the Brookfield Viscometer catalogue gave viscosity in centipoise.

2.1.4 Spreadability

Spreadability was determined by applying an excess of sample within the two glass slides then compressed to uniform thickness by placing 1kg weight for 5 min. Weight (50 gm) was added to the pan. The time required for separating the two slides, i.e. the time in which the upper glass slide moves over the lower glass plate was taken as measure of Spreadability (S).

Spreadability (g.cm/s) (S) = M × (L/T)

Where M = weight tied to upper slide, L = length moved on the glass slide, and T= time taken

2.1.5 Extrudability

Extrudability is the force required to extrude the emulgel from the tube. In this study emulgel extruded from lacquered aluminium collapsible tube on applications of weight in grams required to extrude at 0.5cm ribbon of emulgel in 10sec. For better extrudabitity, more quantity was extruded. For the measurement of extrudability, it was done in triplicate and the average values were calculated. The extradability was then calculated by using the following formula:

Extrudability = weight applied to extrude emulgel from tube (gm)/ Area (cm2)

2.1.6 Centrifugation

This is the parameter measured to evaluate physical stability. Emulgel could be centrifuged at an ambient temperature and 6000 RPM for 10 min to evaluate the system for creaming or phase separation. System could be observed visually for appearance.

2.1.7 Drug content determination

Drug content analysis was determined by dissolving 1 g of gel in 100 ml of phosphate buffer pH 7.4. Filtered to obtain a clear solution. Then 1ml of this solution was transfer to the 100 ml volumetric flask and final volume was made by solvent. Then, Absorbance of prepared solution was measured at 242 nm using UV-visible spectrophotometer. The percentage drug content was calculated. Concentration and drug content can be determined by using the standard plot from the values of absorbance.

2.1.8 In-vitro diffusion (drug release) studies

The experiments were conducted in Franz diffusion cells with a receiver and donor compartment. A suitable size of pre-treated cellophane membrane was mounted in between donor and receptor cells of the Franz diffusion cells (locally fabricated). The receiver compartment contains 15 ml phosphate buffer solution (PBS); PBS pH 7.4 was constantly stirred by magnetic stirrer at 100 rpm and was maintained at a temperature of 37°C throughout the experiments. A

formulation containing equivalent to 20 mg Dexketoprofen trometamol drug was applied homogenously into the donor compartments; 1ml samples were withdrawn from receiver compartment at pre-determined time intervals over 5 hours and immediately replaced with an equal volume of fresh PBS. Samples were assayed for drug content spectrophotometrically at 242nm. The cumulative % drug release was determined. The sink condition was maintained throughout the experiments88.

2.1.9 Stability studies

The emulgel batches were evaluated for their stability according to ICH guidelines for 6 months under three storage conditions - long term (25 ± 2oC/60 ± 5% RH), intermediate (30 ± 2oC/65 ± 5% RH) and accelerated (40 ± 2oC/75 ± 5% RH) storage conditions in the stability chamber respectively. The emulgels were tested for any physical or chemical changes every 2 months.

The results obtained from the experimental studies are documented in the following section under Results and Discussion.

3. RESULT AND DISCUSSION

3.1 Pre-formulation Studies of Dug

3.1.1 Organoleptic properties

Dexketoprofen trometamol was evaluated for its organoleptic characteristics and was found to be true to its specifications. It was white to off white crystalline powder, odorless, and had a characteristic bitter taste.

3.1.2 Solubility

Solubility of Dexketoprofen trometamol was determined as per the procedure given in experimental work. Solvents used were distilled water, methanol, ethanol, chloroform, and DMSO. The results were found to be within the limits and are given in table 2.

Table-2: Solubility of Dexketoprofen trometamol in different solvents

Solvent	Solubility
Distilled water	Freely soluble
Methanol	Sparingly soluble
Ethanol	Slightly soluble
Chloroform	Sparingly soluble
DMSO	Freely soluble

3.1.3 Melting point

It was determined as per the procedure given in preformulation studies in experimental work. The average of three readings was considered as final result and it was found to be 104.94oC. The result complies with the standard specifications for Dexketoprofen trometamol.

3.1.4 Partition coefficient

Average of three readings was calculated and it was found to be: -

Log P = 2.65

This indicated that Dexketoprofen trometamol has an ambient lipophilicity that means it is ideal for topical administration.

3.1.5 Standard curve derivation by UV spectrophotometry

a) Determination of λmax and Plotting Calibration Curve of Dexketoprofen Trometamol

The **λmax** of Dexketoprofen Trometamol was found to be at 242 nm in PBS 7.4 pH. Thus, a calibration curve was plotted using different concentration samples and their respective absorbances at 242nm..

Table-3: Absorbances at different concentrations

Concentration (µg/ml)	Absorbance at 242nm
0	0
10	0.128
20	0.2407
30	0.354
40	0.466
50	0.535
60	0.641
70	0.701
80	0.785
90	0.892
100	0.978

3.1.6 Drug-excipient compatibility studies

In the present study, it was observed that there were no physical as well as chemical interactions between Dexketoprofen trometamol and the excipients used. It was observed that there were no changes in the main peaks in IR spectra of mixture of drug and polymers, which concluded that the drug and excipients used were compatible with each other in order to prepare the formulation.

3.2 Evaluation of Formulated Emulgel Batches

3.2.1 Physical appearance and texture

The formulated emulgels were examined for their color, homogeneity, consistency, and phase separation after 24 hours of preparation. They were white, homogenous, transparent to white to opaque and were viscous gel preparations with a smooth homogeneous appearance. There was no significant phase separation observed in the formulations.

3.2.2 Centrifugation

The prepared emulgels were subjected to centrifugation test to determine the physical stability and there was no phase separation or creaming observed during this test which indicated that the formulations were stable.

3.2.3 Measurement of pH

The pH of the emulgel formulations was in the range of 6.07 to 6.33, which lies in the normal pH range of the skin and would not produce any skin irritation

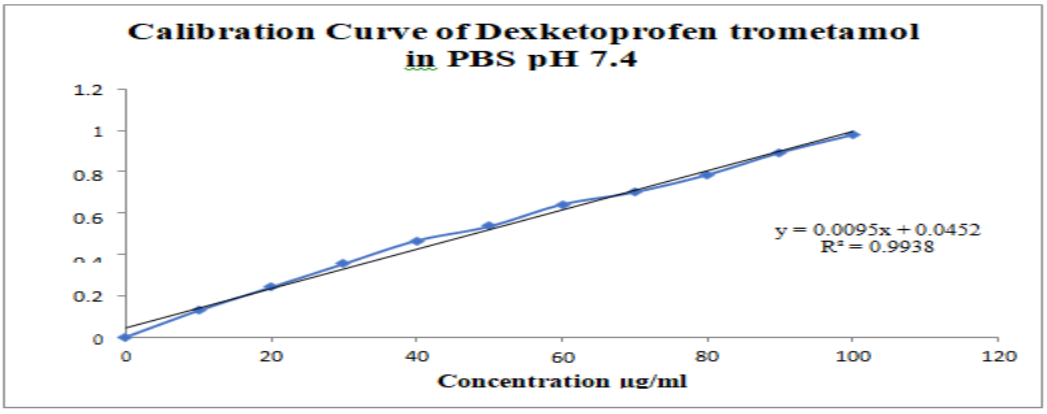

Fig-1: Calibration Curve of Dexketoprofen trometamol in PBS pH 7.4

The viscosity of prepared emulgel was determined at 35°C using a Brookfield viscometer with spindle no. 6 at 50 rpm by Brookfield viscometer. Viscosity of the Emulgel formulations from F1 to F6 is shown in Table-6.

3.2.5 Spreadability

The Spreadability of the Dexketoprofen trometamol emulgels was found to range between 21.56 to 31.56 g.cm/sec, which is indicative of good Spreadability and is tabulated

3.2.6 Extrudability

The extrudability of the formulations ranged from 185-199. The formulation F5 was found to show the best extrudability of 199g/cm2. The values are given in table 6.

3.2.7 Drug content determination

The drug content of the formulations was determined by using standard plot and the values are given in table 6. The values were found within the standard IP limits of 90-110%. Hence, all formulations were acceptable. Formulation F5 was found to have the maximum percentage drug content.

Table-4: pH, Viscosity, Spreadability, Extrudability, and Drug content values of prepared Dexketoprofen trometamol emulgel formulations

Formulationcode	pH	Viscosity (cps)	Spreadability (g.cm/sec)	Extrudability (g/cm^2)	Drug content (%)
F1	6.22	6759	26.23	188	92.85
F2	6.15	7623	27.45	187	93.68
F3	6.33	6895	28.56	189	96.11
F4	6.07	8536	27.36	190	95.31
F5	6.25	5363	31.56	199	98.45
F6	6.11	5956	29.15	196	96.23

3.2.8 In-vitro diffusion (drug release) studies

From the In-vitro studies, it was found that the percentage of drug release after 6 hours ranged between 72% to 94% from all formulations. Formulation F5 followed by F6 released the highest percentage of drug in 6 hours and F1 released the lowest amount. This clearly indicates that ac combination of HPMC and Carbopol 934 (1:1 ratio) showed higher permeation among all permeation enhancers. Also, Carbopol 934. The drug release data is given in table 7. The drug release from formulations was in the order: -

F5 > F6 > F3 > F4 > F2 > F1

Table-5: Drug release data of emulgel formulations

S. No.	Time (hours)	Formulation code and % Cumulative drug release					
		F1	F2	F3	F4	F5	F6
1	1	25.24	30.28	33.02	31.16	41.21	35.14
2	1.5	29.01	35.06	38.14	36.32	48.12	42.22
3	2	34.11	40.89	45.61	42.18	55.65	50.89
4	2.5	40.21	44.25	51.12	47.15	60.87	55.47
5	3	48.05	50.12	58.14	55.95	67.23	62.31
6	3.5	52.16	57.89	65.74	63.02	75.55	68.11
7	4	57.55	56.13	72.11	69.52	80.12	75.46
8	4.5	62.58	66.77	79.65	74.13	82.15	81.23
9	5	66.31	71.25	82.63	77.44	87.69	85.72
10	5.5	68.24	75.14	84.15	80.06	91.47	88.14
11	6	72.65	79.81	86.14	82.33	94.26	91.47

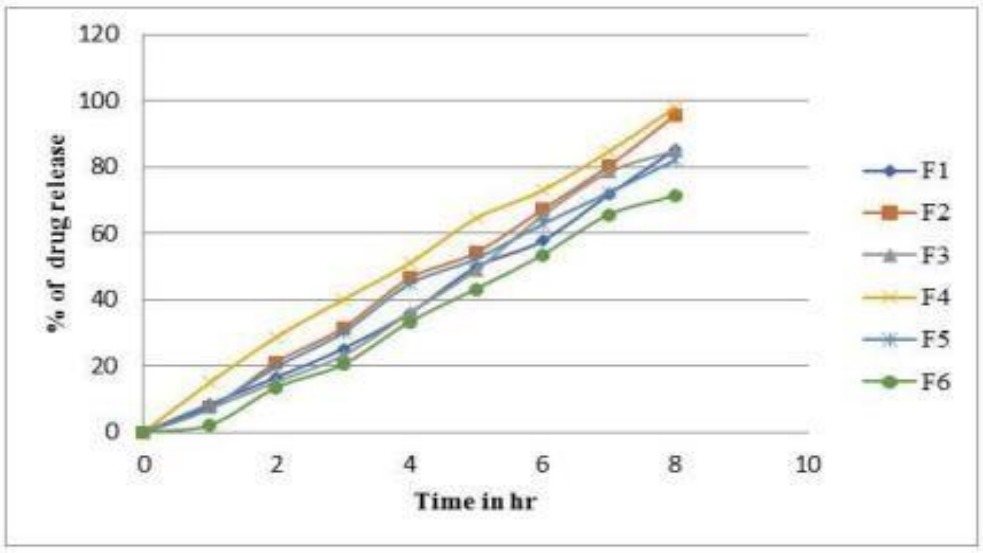

Fig-2: In-vitro drug release data of all formulations of Dexketoprofen trometamol emulgel

3.2.9 Stability studies

All the formulations did not show any significant change in physical appearance as well as in chemical properties under

all conditions of storage and similarly no significant changes in emulgel homogeneity. The results concluded the emulgel batches to be stable in all conditions of storage as per the ICH guidelines.

4.Summary And Conclusion

The formulation and evaluation of Dexketoprofen trometamol emulgel batches using various ingredients was successfully carried out. The results of all the evaluation parameters were determined to be well within the acceptable limits and thus, the investigation work was successfully concluded. The following points were addressed in this work: -

Emulgel is a combinational formulation consisting of emulsion and gel and the type of combination depends upon the nature of drug so that maximum bioavailability can be achieved. The benefits of Emulgel over the traditional topical administration include thixotropic, greaseless, improved spreadibility, easily removable, biodegradable, emollient, and better convenience. Along with this, high stability and improved shelf life of Emulgel is also encouraging the researchers to develop new products belonging to this class(84). Currently, the available topical drug administration technologies are able to deliver the hydrophilic drugs only and the inability to deliver the hydrophobic drugs is one of the major limitations for this approach. Emulgel is one of the recently developed formulations, which is able to deliver both the hydrophilic and hydrophobic drugs. It is closely related to gels, which consist of a colloidal network that holds a large amount of water or hydroalcoholic solution. It provides improved solubility of drugs and hence improved the penetrability of the drug and consider as one of the ideal approaches for topical delivery of drugs. Besides the benefits of gels, it is also unable to deliver the lipophilic drugs and hence Emulgels are developed to overcome this limitation. Structure of skin was also studied to understand the topical drug absorption mechanism of emulgel formulation(85).

Dexketoprofen trometamol is a water-soluble salt of Dexketoprofen and belongs to the class of organic compounds known as benzophenone. It is the dextrorotatory stereoisomer of ketoprofen having a faster onset of action and better therapeutic value. It belongs to the class of non-steroidal anti-inflammatory drugs and is a modified non-selective COX inhibitor having analgesic, antipyretic and anti-inflammatory properties that is available as both oral and parenteral formulations(81, 86). It is available in various countries in Europe, Asia and Latin America. Dexketoprofen trometamol appears to provide similar analgesic efficacy to COX-2 inhibitors when used to treat acute pain, has a rapid onset of action, is well tolerated, and has an opioid-sparing effect when used as part of a multimodal regimen in the acute pain setting(87).

A detailed review of literature was done which encircled studies about emulgels in general, about, topical drug delivery, about Dexketoprofen trometamol, and about human skin. This was followed by a detailed description about the drug and the excipients used in this project work.

Various experimental tests were performed on the drug as well as on the prepared emulgel formulation batches. The tests were performed as per the documented standard procedures and results were found to be within standard limits. Emulgel was concluded to be a successful dosage from for topical delivery of drugs. Out of all the prepared formulations, F5 was found to have the best release rate and maximum drug content. Also, Carbopol 934 was found to be a better permeation enhancer than HPMC. Thus, the present thesis work was successfully carried out.

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